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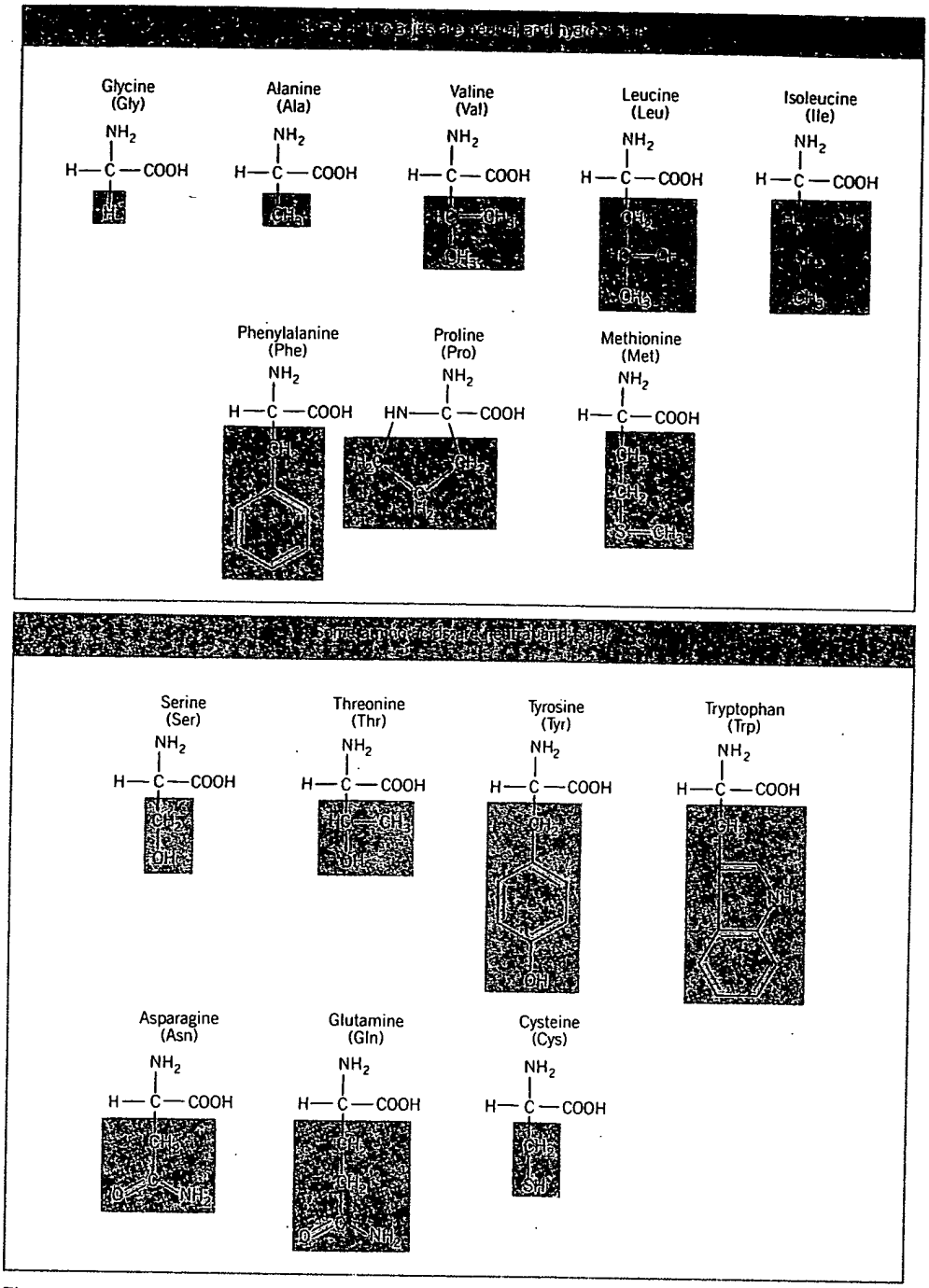

Figure 1.2
Amino acids are classified according to the nature of their side groups.
Each amino acid is known by a three letter abbreviation.

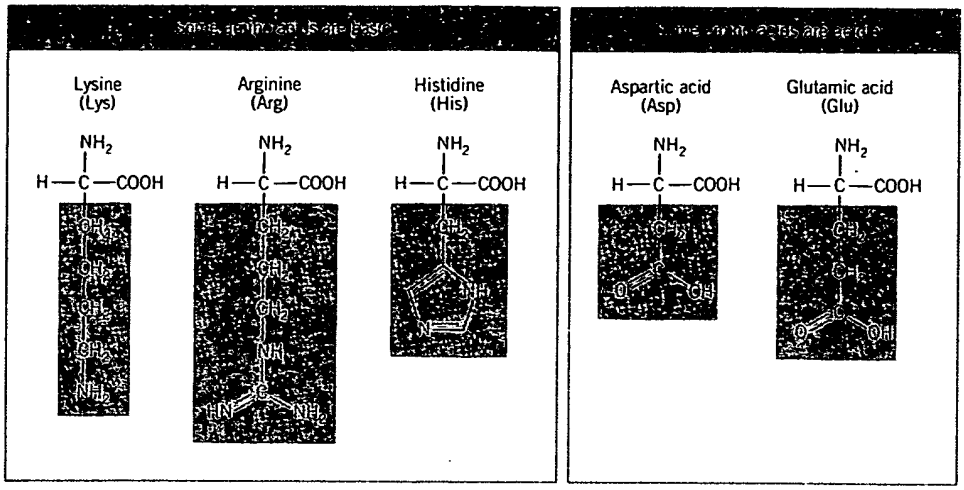

Figure 1.2 (continued)

sometimes a series of alternate conformations). The conformation is described in terms of several levels of structure.

The series of amino acids that constitutes a polypeptide chain comprises its **primary structure.** The **secondary structure** is generated by the folding of the primary sequence, which is made possible by the ability to move freely about bonds of free rotation. Secondary structure refers to the path that the polypeptide backbone of the protein follows in space.

Several types of interactions between amino acids contribute to the acquisition of secondary structure. Both covalent and noncovalent bonds are involved.

In many proteins, one of the important features responsible for establishing the secondary structure is the formation of S—S disulfide "bridges" between two cysteine residues (forming cystine). Each cysteine is separately placed into the polypeptide chain at the appropriate location; the condensation of the two —SH groups into the S—S bridge occurs later, when they are brought into apposition as the chain begins to fold into the correct conformation.

In all proteins, a major force underlying the acquisition of conformation is the formation of noncovalent bonds, in particular ionic interactions between oppositely charged groups (such as acidic and basic amino acids), hydrophobic interactions between amino acids with apolar side-chains, and hydrogen bonds.

Hydrogen bonds are weak electrostatic bonds that occur between a partially negatively charged oxygen atom and a partially positively charged hydrogen atom, as in the examples

$$\begin{array}{lll} \delta^+\ \delta^- & & \delta^+\ \delta^- \\ >C=O & \cdots\cdots\cdots & H—N< \\ \delta^+\ \delta^- & & \delta^+\ \delta^- \\ >C=O & \cdots\cdots\cdots & H—O— \end{array}$$

(The δ indicates the partial nature of the electric charge.) The polarization of the C=O and the N—H or O—H bonds in effect allows the formation of a hydrogen bond between the two groups. The bond takes its name from the fact that the hydrogen atom is to some degree shared between the reacting groups.

Hydrogen bonds are much weaker than covalent bonds, by a factor of more than 10. However, because a large number of hydrogen bonds can be formed in a macromolecule, their overall contribution to the stability of the conformation can be substantial. But the weakness of the individual hydrogen bond (and of other noncovalent bonds) allows them to be broken relatively easily under physiological conditions. This is an important aspect of the function of both proteins and nucleic acids.

Proteins show enormous diversity of form as a result of their ability to generate a huge range of conformations. Certain types of secondary structure are relatively common. Two particularly well known types are the alpha helix and beta sheet.

Hydrogen bonding between groups on the same polypeptide chain may cause the backbone to twist

	1 5 10 15
Anglerfish II	His-Ala-Asp-Gly-Thr-Tyr-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gln-Asp-
Anglerfish I	His-Ala-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Lys-Asp-
Catfish	His-Ala-Asp-Gly-Thr-Tyr-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Gln-Asp-
Salmon	His-Ala-Asp-Gly-Thr-Tyr-Thr-Ser-Asn-Val-Ser-Thr-Tyr-Leu-Gln-Asp-
Daddy Sculpin	His-Ala-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Asn-Asp
	7 10 15 20
Mammalian (Human, Rat, Hamster, Guinea Pig)	His-Ala-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-

	20 25 30
Anglerfish II	Gln-Ala-Ala-Lys-Glu-Phe-Val-Ser-Trp-Leu-Lys-Ala-Gly-Arg-Gly
Anglerfish I	Gln-Ala-Ile-Lys-Asp-Phe-Val-Asp-Arg-Leu-Lys-Ala-Gly-Gln-Val
Catfish	Gln-Ala-Ala-Lys-Asp-Phe-Ile-Thr-Trp-Leu-Lys-Ser-Gly-Gln-Pro-Lys-Pro-Glu (34)
Salmon	Gln-Ala-Ala-Lys-Asp-Phe-Val-Ser-Trp-Leu-Lys-Ser-Gly-Arg-Ala-
Daddy Sculpin	Gln-Ala-Ile-Lys-Asp-Phe-Val-Ala-Lys-Leu-Lys-Ser-Gly-Lys-Val
	25 30 35
Mammalian	Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly

It has been shown that in glucagon, the carboxy-terminal residues are involved in the receptor binding to liver membranes (57) and that amino terminal residues are important for the activation of adenylate cyclase pathway (58,59) leading to increase in cAMP. The amino-terminal histidine in a number of peptides, such as vasoactive intestinal peptide and rat growth hormone releasing hormone has also been shown to be important in the activation of adenylate cyclase (60). Based on these observations, we predict that in the GLP-I the amino terminal residues will be involved in regulation of cAMP levels. Our conclusions are further supported by the conservation of the amino terminal residues amongst GLP-I's during evolution. On the other hand, there is some variation amongst GLP-I's carboxy-terminal residues. Our interpretation of these differences is that like in glucagon, the carboxy-terminal domain of GLP-I's represents the binding domain. Variation in the sequence might reflect structural changes that evolved amongst specific GLP-I receptor(s) on the target tissues.

Proposed analogs to be synthesized.

1. GLP-I(7-35)
2. GLP-I(7-34)
3. GLP-I(7-36) arginine amide